REMARKS

Status of the Claims

Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 were currently pending. Claim 1 has been amended to include a derivative of SEQ ID NO:2 having a conservative amino acid substitution where the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. Support for the amendments to claim 1 can be found, *inter alia*, at paragraphs **[0018]**, **[0040]**, and **[0041]**. Claims 23, 31, 39, 45, 50, 60, and 68 have been written in independent format and claims 31, 39, 45, 50, 60, and 68 were amended similarly to claim 1. No new matter is added by the amendments. The remaining claims have not been further amended. After entry of the amendment, claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 will be pending.

The claims were not rejected over the prior art.

Entry of the amendment and reconsideration in view of the following comments is respectfully requested. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Objection re Informality of Claim 23

Claim 23 has been written in independent format. In view of this amendment, Applicants submit that this objection should be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office stated:

> Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 are directed to all possible chimeric proteins having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence having at least 80% identity with the amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment that binds to an antibody that specifically binds to an amino acid sequence as set forth in SEQ ID NO: 2 and any peptidyl fragment comprising an amino acid sequence having at least 80% identity with the amino acid sequence set forth in SEQ ID NO: 1 and methods of methods of their use, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these enzymes or methods of use of said chimeric protein, by any identifying structural characteristics or properties other than the activity of a nucleotidase, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002).

Applicants respectfully traverse this rejection in light of the amendments to the pending claims, and in view of the revised guidelines concerning compliance with the written description requirement.

Claim 1 is directed to an isolated chimeric protein having the enzymatic activity of a nucleotidase, which chimeric protein comprises, from N-terminus to C-terminus, a first peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence as set forth in SEQ ID NO:1; a second peptidyl fragment comprising the amino acid sequence as set forth in SEQ ID NO:2 or a derivative thereof having a conservative amino acid substitution where the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2; and a third peptidyl fragment comprising an amino acid sequence as set forth in SEQ ID NO:3.

In view of the comments relating to the allowability of claim 23, Applicants do not see how the Office can object to the portions of the claim reciting "a first peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence as set forth in SEQ ID NO:1," a second peptidyl fragment comprising the amino acid sequence as set forth in SEQ ID NO:2," and "a third peptidyl fragment comprising an amino acid sequence as set forth in SEQ ID NO:3."

Applicants assert that conservative amino acid substitutions of amino acid sequences were well-known in the art, and were fully described in the specification at paragraph **[0018]**. A person of ordinary skill in the art could empirically replace an amino acid in SEQ ID NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. This type of testing is further described in the specification, for example at paragraph **[0043]**, which states:

> Assays for enzymatic activities of 3'(2'),5'-bisphosphate nucleotidases are known in the art (*See e.g.*, Murguía et al., *J. Biol. Chem.*, 271(46):29029-33 (1996)). Exemplary methods for phosphatase activity include determining the formation of inorganic phosphate (Pi) and AMP include colorimetric methods (*See, e.g.*, Gumber et al., *Plant Physiol.*, 76:40-44 (1984); Baykov et al., *Anal. Biochem.* 171:266-70 (1988)) and radioactive-labeled substrates (*See, e.g.*, Spiegelberg et al., *J. Biol. Chem.* 274(19):13619-28 (1999); Peng et al., *J. Biol. Chem.* 270(49):29105-29110 (1995)).

A person of skill in the art, reading the specification, would be able to design and test the derivative peptides for the requisite activity.

Furthermore, the art discloses sufficient relevant identifying characteristics such that a person of skill would be able to correlate the structure of SEQ ID NO:2 with the requisite functional activity as described in detail in Example 11B of the written description guidelines.

SEQ ID NO:2 is the Hal2p protein. This protein was known in the art at the time the application was filed, as evidenced by paragraph **[0040]**. Furthermore, the art recognized the functional domains of Hal2p proteins. For example, Albert et al.(*X-ray Structure of Yeast Hal2p, a Major Target of Lithium and Sodium toxicity, and Identification of Framework Interactions Determining Cation Sensitivity*, J. Mol. Biol. (2000) 295:927-938, **Exhibit A**) solved the crystal structure of Hal2p complexed with magnesium, lithium AMP and Pi. Hal2p is a two-domain structure linked at residue 220, containing an N-terminal domain, and a C-terminal domain (*id.,* at page 928, right column). The active site lies between the N-terminal and C-terminal domains, and is capped by a hairpin that includes residues 34-45 (*id.*, page 928 – 929). Albert noted that the crystal structure of members of the Hal2p superfamily has a similar structure, where the metal sties are structurally conserved at the intersection of topologically equivalent secondary structures (*id.,* page 929). Albert found that magnesium appears to occupy sites S1 and S3, lithium occupies site 2; and AMP occupies two pockets in the C-terminal domain (*id.,* page 929). Furthermore, Albert describes residues identified as affecting lithium sensitivity, which correspond to Lys33, Glu72, Asp142, Asp145, and Thr147 in Hal2p (*id.,* page 929, citing to Pollack et al., 1993, Gore et al., 1993, Rees-Milton et al., 1997). So, for example, mutations outside of those residues identified as being important for lithium sensitivity are unlikely to affect the lithium binding activity of the protein. A skilled artisan at the time of the invention would have understood that high conservation of amino acid sequences typically has important functional implications, and therefore highly conserved amino acids within the family should not be mutated if one desires to retain biological function, or alternatively, biological function is more likely to be retained if conservative substitutions are made in these regions. Clearly, a large of amount of structure-function correlation data had been published at the time the application had been filed.

Based on the foregoing discussion of this rather limited selection of prior art, a person skilled in the art would have inferred that, being a member of the family of phosphatases that

hydrolyze PAP to AMP, the Hal2p protein is subject to certain well-established rules with respect to catalytic activity. One of skill in the art upon reviewing Albert (and the other references cited in the specification), would have been provided with adequate guidance with respect to making functional mutants of Hal2p that retain a certain level of 3'(2'),5'-bisphosphonate activity.

In light of the foregoing discussion, Applicants respectfully submit that the specification, combined with the knowledge in the art at the time of the present invention, provides sufficient disclosure to convey to a person skilled in the art that Applicants were in possession of the claimed invention. Accordingly, Applicants respectfully submit that this written description rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 stand rejected under 35 U.S.C. §112, first paragraph. The Office alleged that

> the specification, while being enabling for a chimeric protein having nucleotidase activity comprising the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for any chimeric protein having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence having at least 80% identity with the amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment that binds to an antibody that specifically binds to an amino acid sequence as set forth in SEQ ID NO: 2 and any peptidyl fragment comprising an amino acid sequence having at least 80% identity with the amino acid sequence set forth in SEQ ID NO: 1 and methods of methods of their use, encompassed by these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ

214, 219 (CCPA 1976). MPEP 2164.01. Experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation – time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-7; *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*,802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). MPEP § 2164.01(b) (emphasis added).

In order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). *See also* MPEP §2164.04, 8th ed., rev. 5, Aug. 2006, page 2100-187.

Compliance with 35 U.S.C. § 112, first paragraph enablement does not require that specific portions of any amino acid sequence be identified. However, it should not require undue experimentation to determine those portions of the sequence that are capable of mediating a biological function similar to that mediated by the protein of SEQ ID NO:2. As explained above, "[t]he test of enablement is whether one reasonably skilled in the art could make or use the

invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Telectronics* at 785 (emphasis added). Nothing more than objective enablement is required, and it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Some experimentation is allowed as long as it is not undue.

As an illustration, in the recent *Kubin* appeal stemming from U.S. Appl. No. 09/667,859, the exemplary claim recited "[a]n isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48." The Examiner rejected the claim for lack of enablement. The Board of Patent Appeals and Interferences overturned the enablement rejection while concluding that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine [because] [t]he techniques to do so were well known to those skilled in the art." *Ex parte Kubin*, Appeal No. 2007-0819, at 14 (BPAI May 31, 2007).

As discussed previously, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed. The specification expressly describes methods by which such polypeptides having conservative amino acid mutations can be prepared without any undue experimentation. For example, the specification teaches the types of amino acid substitutions that may be used to achieve functional equivalence (paragraph **[0018]**). Numerous computer programs exist that simplify the task of designing homologous nucleotide sequences that are likely to have similar biological activities through conservative amino acid substitutions. The actual preparation of the nucleic acids that encode such conservative variants also involves routine automated steps. Moreover, paragraph **[0043]** of the specification disclose specific assay protocols that can be used to evaluate the biological activity of mutant recombinant proteins. Testing variants with conservative substitution(s) using the disclosed assays and comparing them to the reference proteins is routine and does not require undue experimentation.

Applicants acknowledge that change of a single amino acid can in some instances alter the activity of a protein. However, it is also true that most such changes have no effect whatsoever on the activity, or at least permit the protein to retain the activity of the referent. Applicants claim only those variants which actually do retain a certain level of 3'(2'),5'-bisphosphonate activity recited in the claims, and thus the claims do not encompass inoperative embodiments. As stated above, assays for these types of biological activity are set forth in the specification in paragraph **[0043]**. Thus, it is very feasible to make an arbitrary change in the protein sequences recited in claim 1 and verify that the variant or fragment retains the desired activity. While it may be unpredictable whether any particular mutant will be successful in retaining activity, it is virtually guaranteed that there will be many instances where such minor changes do result in such retention, and no undue experimentation is required to find them. Accordingly, Applicants believe that the variants recited in the claims are enabled.

Thus, Applicants maintain that the specification provides reasonable guidance to the skilled artisan regarding how to make and use the invention, including providing sufficient guidance on protein structure and sufficient guidance on methods for designing variant proteins having a desired activity. Accordingly, Applicants respectfully submit that the present claims are fully enabled by the specification to overcome the rejection under 35 U.S.C. §112, ¶ 1.

CONCLUSIONS

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 466992001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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